RESPONSE TO OFFICE ACTION

A. Status of the Claims

This application was filed May 31, 1995. The application is a divisional application of 08/292,694, filed August 19, 1994, which is currently pending. Claims 1-46 were cancelled and claims 47-80 were added by a Preliminary Amendment. In subsequent prosecution, claims 47-73 and 75-80 were elected following a Restriction Requirement dated October 29, 1996. In a Response to Office Action dated October 27, 1997, claims 53-58, 60-62, and 68-80 were withdrawn from consideration as non-elected species, and claims 81-90 were added. After all considered claims were rejected, Applicants amended some of the claims and added claims 91-114 in the Response to Office Action dated June 29, 1998. An Office Action dated August 13, 1999 rejected claims 47-49, 51, 59, 63-67, 81, and 83-114, and objected to claims 50, 52, and 82. In the response to the Office Action dated August 13, 1999, claims 47, 49, 59, 63, 66, 84-114 were amended. In the most recent Office Action dated March 2, 2000 (the "Action"), claims 47-51, 53-59, 63, 65-67, 81, and 83-114 are rejected. Thus, claims 47-51, 53-59, 63, 65-67, 81, and 83-114 are the subject of this response. A copy of the pending claims as Applicants believe them to be is included as Appendix A.

B. Claims 47-51, 59, 63, 65-67, 81, and 83-114 Are Enabled

The Action rejects claims 47-51, 59, 63, 65-67, 81, and 83-114 as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. More specifically, it argues that Applicants have not provided working examples of sequences of 30 nucleotides or 10 amino acid peptides, as recited by the rejected claims, and that no guidance has been provided about how to predict which sequences would code for the receptors or about how to predict binding domains

other than the second extracellular loop of the kappa receptor. It concludes that the breadth of the claims is too large with regard to the number of possible chimeric opioid receptors and that undue experimentation would be required to make and use recombinant opioid receptors comprising at least 30 contiguous bases of SEQ ID NO:1 or 11. Applicants respectfully traverse this rejection.

1. The Specification Provides Sufficient Guidance and Numerous Working Examples

"The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" MPEP 2164.08 (citing *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q. 1510, 1513 (Fed. Cir. 1993)). Applicants contend that the Specification clearly teaches how to make and use "recombinant opioid receptor polypeptides encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1" or "SEQ ID NO:11."

The Specification is replete with descriptions of various chimeric molecules that comprise "at least 30 contiguous bases of SEQ ID NO:1 or 11." For example, the disclosure describes a chimeric molecule containing three regions: N-terminal and C-terminal fragments from SSTR1, a subtype of the somatostatin receptor, and the third extracellular loop from a kappa opioid receptor. The third extracellular loop, depicted for example in SEQ ID NO:14, is 28 amino acids in length, and is a candidate G protein coupling domain. *See* Specification at least at page 97. The specification also describes the following chimeras: 1) the N-terminal portion of a kappa opioid receptor (amino acids 1-74) and the C-terminal portion of the delta opioid receptor (amino acids 65-372) (page 87); 2) residues 1-78 of the kappa opioid receptor with residues 70-372 of a delta opioid receptor (FIG 10A and B); 3). residues 1-69 of a delta opioid receptor and residues 79-380 of a kappa opioid receptor (FIG. 10A and B); and 4)

residues 1-74 of a kappa opioid receptor and residues 65-372 of a delta opioid receptor (page 91); residues 1-64 of a delta opioid receptor and residues 75-380 of a kappa opioid receptor (page 90). Each of these chimeric receptors is a working example demonstrating the rejected claims. With these descriptions of various chimeras are protocols and strategies for constructing such molecules, including PCR primers that can be used to amplify particular regions, as well as primers that can be used to mutate specific segments of DNA. *See e.g.,* Specification at 86-101. Moreover, the specification indicates which amino acids encode the four extracellular domains of the kappa opioid receptor, for example, residues 197-220 correspond to the third extracellular domain and residues 300-311 correspond to the fourth extracellular domain, and that both of these are possible candidates for interacting with agonists or antagonists. *See* Specification at page 91.

Applicants also point out that the claims do not require "ligand binding." Instead, the claim are directed at processes for "screening a substance for its ability to interact with an opioid receptor." The Specification also teaches that peptides can be used to generate antibodies. *See e.g.,* Specification at page 107. The technology available at the time the invention was filed would allow such peptides to be prepared using recombinant DNA. Consequently, the disclosure in the application that portions of the kappa opioid receptor can interact with a protein, *i.e.,* an antibody, further supports the contention that the Specification enables the claimed invention. SEQ ID NO:39 is 14 residues in length and would correspond to a DNA fragment of 42 bases, which would meet the limitation of "at least 30 contiguous bases of SEQ ID NO:1." This peptide was used to generate antisera, which was then tested for its ability to recognize kappa opioid receptor. The specificity of the peptide was further confirmed using competitive binding experiments with the peptide. Therefore, the Specification, combined with the knowledge of

recombinant DNA that one of skill in the art would possess, allows a person to practice the claimed invention because the antibody and the assays involving them qualify as a process for screening for a "substance for its ability to interact with an opioid receptor." Moreover, Applicants contend that the antibody binding assays provide an example where the second extracellular loop of the kappa opioid receptor is not required for binding another polypeptide, since the claim is not limited to the identification of agonists and antagonists.

In view of the above, contrary to the Action's assertion, the Specification provides numerous working examples that fulfill the limitations of the rejected claims. The claims recite a polypeptide encoded by "*at least* 30 contiguous nucleotides." In addition to disclosure of chimeric molecules including various lengths of kappa opioid receptor sequences, the Specification teaches how to introduce a specific alteration into the DNA sequence, and consequently the amino acid sequence using PCR and primers corresponding to the alteration. *See e.g.,* Specification at page 87, line 28; and page 91, line 30.

The test for determining whether the amount of experimentation required to enable the embodiments of a claim is not merely quantitative; rather, "a considerable amount of experimentation is permissible..." *See In re Forman*, 230 USPQ 546, 547 (BPAI 1986). Given the extensive teaching in the specification—the working examples of various chimeric molecules and peptide segments, numerous assays to determine whether a compound binds to a kappa opioid receptor; naming agonist and antagonist compounds that can be used as controls or standards; and DNA and protein sequences—the amount of experimentation required to practice the claimed invention is not undue, and therefore, meets the standard for enablement of the claims.

2. The Sequence Listing Indicates Coding Region of DNA

The Action contends that there is no discussion in the specification as to which groups of 30 nucleotides or SEQ ID NO: 1 or SEQ ID NO:11 will translate into a functional opioid polypeptide that can bind ligands. Applicants dispute this contention and point to the Sequence Listing containing SEQ ID NO:1. and SEQ ID NO:11 starting at pages 195 and 207 of the Specification. The listing for both SEQ ID NOS: 1 and 11 depicts a nucleic acid sequence, and directly underneath it is the translated amino acid sequence, indicating which portions of the nucleic acid sequence encode the opioid polypeptide. Thus, the Action is mistaken that there is no indication in the specification about which sequences encode a kappa opioid receptor.

3. The Cited References Are Irrelevant or Support Applicants' Position

The Action cites three references, George *et al.* (1988) ("George"), Rudinger (1976), and Cunningham and Wells (1989) ("Cunningham") in regard to its enablement rejection.

Applicants contend George does not support the Action's contention that because SEQ ID NO:2 is 380 amino acids long and SEQ ID NO:12 is 295 amino acids in length, it would require undue experimentation to determine which segments of at least 10 amino acids would be sufficient to bind kappa opioid ligand. George is quoted as saying," Sequence comparison methods will not be able to assess biological relatedness until the structure/function problem is more clearly understood." The Action neglects to mention that the sentences following the quoted passage read: "These techniques, however, provide extremely powerful tools for identifying possible relationships between biomolecules. They can give strong supporting evidence for such a relationship and can aid the investigator in formulating hypotheses and in suggesting possible experimental approaches." (p. 145-46). Applicants note that there is very high identity between SEQ ID NO:2 and SEQ ID NO:12, as shown in FIG. 4. In this case, it is unequivocal that sequence alignment demonstrates that these two sequences are related, and thus,

George's comment about being unable to assess biological relatedness is not applicable to the sequences of SEQ ID NO:2 and 12. Instead the alignment of these sequences proves the power of this technique, as is noted by George. Thus, the George reference does not support the Action's contention.

As for the Rudinger reference, Applicants point out that that reference was published *more than 13 years before the application was filed.* In a field such as molecular biology, technological advances are plentiful and ongoing. Recombinant DNA protocols that were routine at the time the present application was filed were probably far from trivial in 1979. Applicants do not doubt that "the significance of particular amino acids and sequences for different aspects of biological activity...must be determined from case to case by painstaking experimental study" in 1979. Instead, Applicants refute that statement's applicability to the state of the art in 1993, when the priority application was filed, particularly with respect to sequences with such high identity at the amino acid level. Kits for mutagenizing cDNAs, resulting in mutated proteins, are commercially and readily available, as is demonstrated by the Specification, for example, at page 91 ("Altered Site™ in vitro Mutagenesis System" from Promega). The disclosure of the present application also shows how chimeric molecules can be used to identify regions that mediate protein interactions, which was not a novel methodological approach at that time. *See* Raynor and Reisine, 1989 (cited in Specification at page 94). The Specification provides evidence that "painstaking experimental study" is not required to practice the claimed invention with the teaching of the Specification and the knowledge available to one of ordinary skill in the art at the time the application was filed. Consequently, this reference is of no the relevance to enablement issues surrounding the present application.

The Action cites Cunningham as showing that one amino acid change in the polypeptide sequence of human growth hormone dramatically altered its binding affinity for the human growth hormone receptor. There is no suggestion in the reference, however, that this observation is relevant to other molecules such as opioid receptors. Further, the identity between SEQ ID NO:2 and NO:12 is pertinent because one of skill in the art appreciates that identity between related sequences suggest conservation of a particular amino acid. The content of this reference is distinguishable from the present situation. In the present situation, the issue is whether the identity demonstrated between the same molecules, but from different species, supports the contention that guidance with regard to one sequence is apposite with respect the other sequence from an enablement standpoint. In the Cunningham reference, such a sequence comparison was not involved. It mentions comparing sequences between members of a family of hormones (*i.e.,* different molecules), but the purpose of those comparisons is to identify *divergent* sequences that correspond to the binding domains of the different molecules, which the authors assert were "largely inconclusive." (page 1083). The identify between molecules in the present application suggests the regions in the molecules are comparable and the Cunningham reference says nothing to dispute that.

Finally, even if a single amino acid change could alter binding affinity, determining whether this would be true for a particular amino acid change is routine since the Specification provides guidance about recombinant DNA techniques, assays for measuring binding, compounds that bind the opioid receptors, and examples of binding domains. Thus the Cunningham reference does not refute Applicants argument that the information about SEQ ID NO1 is relevant to an understanding of SEQ ID NO:11.

Therefore, the claims reciting at least 30 bases of SEQ ID NO:1 or 11 are enabled because the Specification provides ample guidance about chimeric molecules and kappa opioid receptors encoded by at least 30 bases of the recited SEQ ID Nos. and that none of the cited references provides evidence to dispute this conclusion

4. Claim Amendments Are Appreciated But Are Not Necessary

Applicants appreciate the Examiner's suggestion to amend the claims to recite "A process of screening a substance for its ability to interact with an opioid receptor, as defined by subsequent step (a), said process comprising the steps of...." However, Applicants believe the claim is presently allowable without the amendment.

As an initial matter, the amendments do not address any enablement issues. Furthermore, Applicants also respectfully point out that the amendment is redundant as a preamble for a process claim is necessarily limited by recitations of steps that follow the preamble. Applicants also respectfully note that the amendment would not introduce any additional limitations into the claim, and instead, would only serve to render the claim more difficult to comprehend. The Action appears to promote form over substance. Finally, with respect to substituting "said" for "the," Applicants submit that such an amendment is unnecessary as the two terms are interchangeable according to patent law. For the sake of consistency ("the" is used throughout all of the claims), as well as clarity, Applicants prefer to keep the language as it is.

Therefore, Applicants appreciate the suggestion made by the Examiner, but will not amend the claims at this time to reflect the suggestion; however, in the interests of furthering prosecution of this case, Applicants remain open to discuss this issue.

C. Claims 47, 84, 86, 88, 90, and 97-101 Are Patentable over Evans *et al.*

The Action rejects claims 47, 84, 86, 88, 90, and 97-101 under 35 U.S.C. § 102 (e) as being unpatentable over Evans *et al.* (U.S. Patent No. 5,985,600 ("the '600 patent")), which is

alleged to disclose an opioid receptor that is 100% identical to 245 contiguous bases of SEQ ID NO:11 (shown in Sequence Comparison A). Applicants respectfully traverse this rejection on two grounds: first, the cited reference of Evans *et al* does not teach the invention, and second, the foreign application of Evans *et al.* is not available as prior art.

Patent law under 35 U.S.C. § 102 (e) states a person may be entitled to a patent unless "the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent...." The '600 of Evans *et al.* simply does not teach SEQ ID NO:11 because this sequence is **not** disclosed in the patent. In fact, the sequence identified in Sequence Comparison A is not contained in the '600 patent.

Sequence Comparison A does not identify the '600 patent as the source of the sequence information, but instead identifies foreign application WO9404552 (Exhibit B). The filing date of the present application is August 19, 1994, while the publication date of WO9404552 is March 3, 1994, which unequivocally removes the published foreign application as prior art under 35 U.S.C. § 102 (b). Furthermore, this present application claims priority to PCT/US94/05747, filed May 20, 1995, which claims priority to U.S. Serial No. 08/147,592 ('592), filed on November 11, 1993. Since the '592 application contains the sequence identified in Sequence Comparison A, and it was filed before the publication date of WO9404552, Applicants contend WO9404552 is also not prior art under 35 U.S.C. § 102 (a).

Moreover, Applicants note that while WO9404552 claims priority to U.S. Serial No. 929,200, which is the parent application of the '600 patent, it clearly cannot claim priority to the parent application with respect to the sequence identified in Sequence Comparison A since it is not disclosed in the priority document (based on the disclosure of the '600 patent).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Because the sequence is not disclosed in the '600 patent, the cited reference does not teach an element of the rejected claims. Therefore, the Evans *et al.* '600 patent does not anticipate claims 47, 84, 86, 88, 90, and 97-101 under 35 U.S.C. § 102 (e) and respectfully request that the rejection be withdrawn.

D. Claims 48-51 Are Nonobvious over Evans *et al.* and Frielle *et al.*

The Action rejects claims 48-51 under 35 U.S.C. § 103 (a) as being unpatentable over Evans *et al.* ('600 patent) and further in view of Frielle *et al.* ("Frielle"). The '600 patent is alleged to teach an opioid receptor that is 100% identical to 245 contiguous bases of SEQ ID NO:11 and disclose methods of expressing this polypeptide in a host cell and of screening a substance's ability to interact with the receptor. The Action contends that Frielle teaches the production of chimeric G protein-coupled receptors and the use of these chimeras in binding assays. The Action also claims that "the motivation for producing and using chimeric kappa opioid receptors would be that it is a very efficient method of determining the ligand binding domains of a receptor." It further contends that it would have been obvious to modify the ligand binding assay of the '600 patent by using chimeric kappa opioid receptors produced by the method of constructing another G protein-coupled receptor chimera. Applicants respectfully traverse this rejection.

Three basic criteria must be met to establish a *prima facie* case of obviousness:

(1) "there must be some suggestion of motivation, either in the references themselves or in the knowledge generally available to

one of ordinary skill in the art, to modify the reference or to combine reference teachings";

(2) "there must be a reasonable expectation of success"; and

(3) "the prior art reference (or references when combined) must teach or suggest all the claim limitations."

MPEP §2142.

Two of these three criteria have not been satisfied, and therefore, that a valid *prima facie* case has not been made. First, Applicants submit that the cited references do not teach or suggest all of the claim limitations because, as discussed above, the patent of Evans *et al.*, the '600 patent, does not teach the sequence identified in the present application as SEQ ID NO:11. The publication identified in Sequence Comparison A is not the '600 patent, but is WO 94/04552, which was published after the filing date of this application's priority application. The Action relies on the '600 for its teaching of SEQ ID NO:11, which is recited in the rejected claims. Without the sequence of SEQ ID NO:11, the combination of references fails to teach or suggest all the limitations of the rejected claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Second, Applicants refute that a valid *prima facie* case of obviousness has been made because contrary to the Action's assertion, the requisite motivation is lacking. The Action contends the motivation is derived from the fact that using chimeric opioid receptors is a very efficient method of determining the ligand binding domains of a receptor. However, instead of motivation to produce the claimed invention, Federal Circuit caselaw requires motivation *to combine references*. "To combine references (A) and (B) properly to reach the conclusion that the subject matter of a patent would have been obvious, case law requires that there must be some teaching, suggestion, or inference in either reference (A) or (B), or both, or knowledge generally available to one of ordinary skill in the relevant art that would lead one skilled in the

art to combine the relevant teachings of references (A) and (B)." *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 U.S.P.Q. 657 (Fed. Cir. 1985); *see also* MPEP § 2143.01 ("[I]t is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification.") (citing *In re Linter*, 458 F.2d 1013, 1016, 173 U.S.P.Q. 560, 562 (CCPA 1972)). Therefore, Applicants assert that the basis for the motivation required for a *prima facie* obviousness case is deficient, and consequently, respectfully request this rejection be withdrawn.

E. Claims 59, 63-66, and 109-113 Are Nonobvious under 35 U.S.C. § 103 (a)

The Action rejects claims 59, 63-66, and 109-113 under 35 U.S.C. § 103 (a) as being unpatentable over Evans *et al.* ("the '600 patent") and further in view of Liggett *et al.* ("Liggett"). The '600 patent is alleged to teach an opioid receptor that is 100% identical to 245 contiguous bases of SEQ ID NO:11 and disclose methods of expressing this polypeptide in a host cell and of screening a substance's ability to interact with the receptor. The Action contends that Liggett teaches the production of chimeric G protein-coupled receptors and the identification of agonists of these chimeras. Once again, the motivation is said to be that producing and using chimeric kappa opioid receptors is a very efficient method of determining the agonist binding domains of a receptor. The Action concludes that it would have been obvious to modify the functional assay described in the '600 patent by using chimeric kappa opioid receptors produced by the method of constructing another G protein-coupled receptor chimera and identifying agonists of this receptor, as taught by Liggett. Applicants respectfully traverse this rejection.

Applicants contend that this rejection as well fails to satisfy two of the three requirements for a valid *prima facie* case of obviousness. The '600 patent does not teach the nucleic acid sequence identified and recited in the claims as SEQ ID NO:11. Without the sequence of SEQ

ID NO:11, the combination of references fails to teach or suggest all the limitations of the rejected claims, as is required for a *prima facie* case of obviousness. *See* MPEP §2142.

Also, Applicants argue that motivation to combine the references is lacking. The Action's assertion that the motivation derives from the fact that producing and using chimeric kappa opioid receptors in an assay to determine agonist binding is misplaced. Patent law requires, however, that the cited references must suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process. *See In re Vaeck*, 20 U.S.P.Q. 2d 1438, 1443 (Fed. Cir. 1991) *citing In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). Applicants submit that this type of motivation is lacking in the combination of references. Consequently, Applicants respectfully request that this rejection be withdrawn.

F. Conclusion

Applicants believe that the present document is a full and complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance and such favorable Action is respectfully requested. Should the Examiner have any further questions or comments, or believe that certain clarifications might more readily progress the present application to issuance, a telephone call to the undersigned Applicants' representative at (512) 418-3081 is earnestly solicited.

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